

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT  
INFRINGEMENT LITIGATION

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C.A. No. 05-356-KAJ  
(consolidated)

**NOTICE OF DEPOSITION AND SUBPOENA OF  
BRISTOL-MYERS SQUIBB COMPANY PURSUANT TO  
FEDERAL RULE OF CIVIL PROCEDURE 45**

**PLEASE TAKE NOTICE** that, pursuant to Rule 45 of the Federal Rules of Civil Procedure, plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Janssen") will take the deposition upon oral examination of Bristol-Myers Squibb Company, at the offices of Esquire Deposition Services, 216 E. 45<sup>th</sup> Street, 8<sup>th</sup> Fl., New York, NY 10017-3304, beginning at 10:00 A.M. on June 9, 2006.

NOTICE IS FURTHER GIVEN THAT the deposition will be recorded stenographically through instant visual display of testimony (real-time), by certified shorthand reporter and notary public or such other person authorized to administer oaths under the laws of the United States, and shall continue from day to day until completed. This deposition will be videotaped.

NOTICE IS FURTHER GIVEN THAT Bristol-Myers Squibb Company is instructed to produce documents, identified in the attached Subpoena, at the offices of Esquire Deposition Services, 216 E. 45<sup>th</sup> Street, 8<sup>th</sup> Fl., New York, NY 10017-3304 by 10:00 A.M. on June 5, 2006.

NOTICE IS FURTHER GIVEN THAT pursuant to the Federal Rules of Civil Procedure, Janssen will serve upon Bristol-Myers Squibb Company a Subpoena in a Civil Case. Attached hereto as Exhibit A is a true and correct copy of that Subpoena.

# EXHIBIT A

A088 Subpoena in a Civil Case

Issued by the  
**United States District Court**

SOUTHERN DISTRICT OF NEW YORK

IN RE: '318 PATENT INFRINGEMENT  
 LITIGATION

**SUBPOENA IN A CIVIL CASE**

Case Number:<sup>1</sup> C.A. No. 05-356-KAJ (consolidated)  
 (District of Delaware)

TO: Bristol-Myers Squibb Company  
 345 Park Ave.  
 New York, NY 10154

☐ YOU ARE COMMANDED to appear in the United States District court at the place, date, and time specified below to testify in the above case.

PLACE OF TESTIMONY

COURTROOM

DATE AND TIME

☒ YOU ARE COMMANDED to appear at the place, date, and time specified below to testify at the taking of a deposition in the above case.  
 Please See Schedule A Attached

PLACE OF DEPOSITION Recording Method: By stenographer and videotape

DATE AND TIME

Esquire Deposition Services, 216 E. 45th Street, 8th FL, New York, New York 10017-3304

June 9, 2006 at 10:00 a.m.

☒ YOU ARE COMMANDED to produce and permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects):  
 Please See Schedule B Attached

PLACE

DATE AND TIME

Esquire Deposition Services, 216 E. 45th Street, 8th FL, New York, New York 10017-3304

June 5, 2006 at 10:00 a.m.

☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below.

PREMISES

DATE AND TIME

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER'S SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)  
 Attorney for Plaintiffs Janssen Pharmaceutica N.V., Janssen L.P., and Synaptech, Inc.

DATE AND TIME

May 26, 2006

ISSUING OFFICER'S NAME, ADDRESS AND PHONE NUMBER

Tiffany Geyer Lydon  
 Ashby & Geddes  
 222 Delaware Avenue, 17th Floor  
 Wilmington, DE 19899  
 Tel: 302-654-1888

(See Rule 45, Federal Rules of Civil Procedure, Parts C&D on next page)

<sup>1</sup> If action is pending in district other than district of issuance, state district under case number.

A088 Subpoena in a Civil Case

**PROOF OF SERVICE**

DATE	PLACE
SERVED	
SERVED ON (PRINT NAME)	MANNER OF SERVICE
SERVED BY (PRINT NAME)	TITLE

**DECLARATION OF SERVER**

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Proof of Service is true and correct.

Executed on

DATE

SIGNATURE OF SERVER

ADDRESS OF SERVER

**Rule 45, Federal Rules of Civil Procedure, Parts C&D****(c) PROTECTION OF PERSONS SUBJECT TO SUBPOENAS.**

(1) A party or an attorney responsible for the issuance and service of a subpoena shall take reasonable steps to avoid imposing undue burden or expense on a person subject to that subpoena. The court on behalf of which the subpoena was issued shall enforce this duty and impose upon the party or attorney in breach of this duty an appropriate sanction which may include, but is not limited to, lost earnings and reasonable attorney's fee.

(2)(A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(2)(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice to the person commanded to produce, move at any time for an order to compel the production. Such an order to compel production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3) (A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

- (i) fails to allow reasonable time for compliance,
- (ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to

the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden

(3)(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial, the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena, or, if the party in whose behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

**(d) DUTIES IN RESPONDING TO SUBPOENA.**

(1) A person responding to a subpoena to produce documents shall produce them as they are kept in the usual course of business or shall organize and label them to correspond with the categories in the demand.

(2) When information subject to a subpoena is withheld on a claim that it is privileged or subject to protection as trial preparation materials, the claim shall be made expressly and shall be supported by a description of the nature of the documents, communications, or things not produced that is sufficient to enable the demanding party to contest the claim.

**SCHEDULE A**

**DEFINITIONS**

1. “Synaptech” shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including without limitation Bonnie M. Davis, M.D. and Synaptec, Inc.

2. “Dr. Bonnie Davis” refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.

3. “You,” “your,” “yours,” or “Bristol-Myers Squibb” shall mean Bristol-Myers Squibb Company and all of Bristol-Myers Squibb Company’s corporate parents, corporate predecessors and past or present subsidiaries, including and without limitation to E.R. Squibb & Sons, affiliates, divisions, departments, officers, directors, principals, agents, employees and any individuals or entities that at any time have acted or purported to act on behalf of Bristol-Myers Squibb Company or its successors.

4. “Communication” and “communications” mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. “Concerning” means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. “Document” means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or

nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term “document” includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. “Person” and “persons” mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. “Alzheimer’s Disease” means any diagnosis, illness, or ailment described as being of the Alzheimer’s type, including without limitation Senile Dementia of the Alzheimer’s Type, and/or Alzheimer’s Dementia.

9. “318 patent” means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. “Galantamine” includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives “and” and “or” shall be construed either disjunctively or conjunctively as

necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, “all” shall include “any” and vice versa, and “each” shall include “every” and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

### **TOPICS**

1. The names and responsibilities of all persons who were involved in any evaluation, consideration or discussion by or on behalf of Bristol-Myers Squibb to license, market or develop the ‘318 patent and the contributions made by them in any evaluation, consideration or discussion by or on behalf of Bristol-Myers Squibb to license, market or develop the ‘318 patent.

2. The names and responsibilities of all persons who were involved in any evaluation, consideration, or discussion by or on behalf of Bristol-Myers Squibb of galantamine as a treatment for Alzheimer’s Disease, and the contributions made by them in any evaluation, consideration or discussion by or on behalf of Bristol-Myers Squibb of galantamine as a treatment for Alzheimer’s Disease.

3. All negotiations or communication by or on behalf of Bristol-Myers Squibb and Synaptech or Dr. Bonnie Davis regarding the ‘318 patent.

4. All negotiations or communication by or on behalf of Bristol-Myers Squibb and Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer’s Disease.

5. The May 22, 1987, letter from John Richards to R.W. Michael, attached hereto as Exhibit 2.

6. The August 3, 1987, letter from Bonnie M. Davis, M.D. to Scott Reynes, M.D., Ph. D., attached hereto as Exhibit 3, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that “a prompt reply indicated no interest.”

7. The September 8, 1987, letter from Scott A. Reynes, M.D, Ph. D, attached hereto as Exhibit 4, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that “we have decided to reconsider galanthamine as a potential licensing-in candidate.”

8. The September 30, 1987, letter from Gary A. King, Ph. D, attached hereto as Exhibit 5, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that “galanthamine HBr cannot be considered for in-licensing at this time ... due to its very early stage of development and the fact that Squibb is not prepared to undertake the very extensive development work that would be required to take this drug into clinical trials.”

9. The February 24, 1989, letter from Bonnie M. Davis, M.D., to Gary A. King, Ph.D attached hereto as Exhibit 6.

10. The October 6, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 7, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter regarding “Bristol-Myer Squibb’s interest in galanthamine.”

11. The October 10, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 8, including without limitation the meaning of, basis for, and any evaluation or

analysis concerning the statement set forth in the letter regarding “[o]ur meeting on Thursday, October 12, at 10:30.”

12. The December 21, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 9, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that “the therapeutic benefit and long term safety and tolerability of galanthamine is still a matter for speculation.”

13. Any evaluation or analysis conducted by or on behalf of Bristol-Myers Squibb concerning galantamine as a treatment for Alzheimer’s Disease.

14. All communications or discussions between Bristol-Myers Squibb and any other person regarding the ‘318 patent.

### **SCHEDULE B**

Pursuant to Rule 45 of the Federal Rules of Civil Procedure, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptech, Inc. hereby propound this subpoena on Bristol-Myers Squibb Company. This subpoena calls for you to produce the documents described under the heading “Requests for Production of Documents” below, in accordance with the following “Definitions” and “Instructions.”

### **DEFINITIONS**

Notwithstanding any definition set forth below, each word, term, or phrase used in these Requests is intended to have the broadest meaning permitted under the Federal Rules of Civil Procedure. The following definitions and rules on construction apply to the Requests:

1. “Synaptech” shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including but not limited to Bonnie M. Davis, M.D.
2. “Dr. Bonnie Davis” refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.
3. “You,” “your,” “yours,” or “Bristol-Myers Squibb” shall mean Bristol-Myers Squibb Company and all of Bristol-Myers Squibb Company’s corporate parents, corporate predecessors and past or present subsidiaries, including and without limitation to E.R. Squibb & Sons, affiliates, divisions, departments, officers, directors, principals, agents,

employees and any individuals or entities that at any time have acted or purported to act on behalf of Bristol-Myers Squibb Company or its successors.

4. “Communication” and “communications” mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. “Concerning” means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. “Document” means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term “document” includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. “Person” and “persons” mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. “Alzheimer’s Disease” means any diagnosis, illness, or ailment described as being of the Alzheimer’s type, including without limitation Senile Dementia of the Alzheimer’s Type, and/or Alzheimer’s Dementia.

9. “318 patent” means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. “Galantamine” includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives “and” and “or” shall be construed either disjunctively or conjunctively as necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, “all” shall include “any” and vice versa, and “each” shall include “every” and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

### **INSTRUCTIONS**

1. The response to each Request shall include all documents within your possession, custody, or control. The phrase “possession, custody, or control” means a document in your physical custody; or, that you own in whole or in part; or, have a right by contract, statute or otherwise to use, inspect, examine or copy on any terms; have an understanding, express or implied, that you may use, inspect, examine or copy on any terms; or you have, as a practical matter, the ability to use, inspect, examine or copy such document.

2. If any document or tangible thing that would have been responsive to the Requests below has been destroyed or is no longer in your possession, custody or control, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); and (ii) states the date of, and identity of the person responsible for, its destruction, loss, transfer, or other action by which the document or tangible thing left your possession, custody or control.

3. The response to each Request shall state, with respect to each item or category, that inspection and related activities will be permitted as requested, unless the Request is objected to, in which event the reasons for objection shall be stated. If objection is made to part of an item or category, the part shall be specified. Any such objection shall not extend the time within which you must otherwise answer or respond to a Request to which no specific objection has been made.

4. If you contend that an otherwise discoverable document would be excludable from production, state the reasons for such objection or grounds for exclusion and identify each person having knowledge of the factual basis, if any, on which the objection or ground is asserted.

5. If any document that would have been responsive to any of the Requests below is not produced because of a claim of privilege or immunity, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); (ii) identifies the name and position of each person to whom a copy was furnished, and each person to whom the original or a copy was shown; (iii) states the general subject matter of each document; (iv) identifies the Request to which the withheld document is responsive; and (v) states the ground on which each document is asserted to be privileged or immune from disclosure. Any attachment to an allegedly privileged or immune document shall be produced unless you contend that the attachment is also privileged or immune, in which case the information specified in the previous sentence shall be separately provided for each such attachment.

6. If there is any question as to the meaning of any part of these Requests, or an issue as to whether production of responsive documents would impose an undue burden, counsel for the Plaintiff should be contacted promptly.

7. You may produce legible, complete, and exact copies of the original documents, provided that the originals be made available for inspection upon request by counsel for the Plaintiff.

8. You are requested to respond in writing to the following Requests, and produce the requested documents for inspection and copying, at the time, date, and location set forth in the subpoena.

**REQUESTS FOR PRODUCTION OF DOCUMENTS**

1. All documents concerning any evaluation, analysis, consideration or discussion to license, market or develop the '318 patent or a '318 patent product.
2. All documents concerning any evaluation, analysis, consideration, or discussion of galantamine as a treatment for Alzheimer's Disease.
3. All documents concerning communications or discussions between you and Synaptech or Dr. Bonnie Davis regarding the '318 patent.
4. All documents concerning communication between you and Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer's Disease.
5. All documents concerning the May 22, 1987, letter from John Richards to R.W. Michael, attached hereto as Exhibit 2.
6. All documents concerning the August 3, 1987, letter from Bonnie M. Davis, M.D. to Scott Reynes, M.D., Ph. D., attached hereto as Exhibit 3, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "a prompt reply indicated no interest."
7. All documents concerning the September 8, 1987, letter from Scott A. Reynes, M.D, Ph. D, attached hereto as Exhibit 4, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "we have decided to reconsider galanthamine as a potential licensing-in candidate."
8. All documents concerning the September 30, 1987, letter from Gary A. King, Ph. D, attached hereto as Exhibit 5, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "galanthamine HBr cannot be considered for in-licensing at this time ... due to its very early

stage of development and the fact that Squibb is not prepared to undertake the very extensive development work that would be required to take this drug into clinical trials.”

9. All documents concerning the February 24, 1989, letter from Bonnie M. Davis, M.D., to Gary A. King, Ph.D attached hereto as Exhibit 6.

10. All documents concerning the October 6, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 7, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter regarding “Bristol-Myer Squibb’s interest in galanthamine.”

11. All documents concerning the October 10, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 8, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter regarding “[o]ur meeting on Thursday, October 12, at 10:30.”

12. All documents concerning the December 21, 1989, letter from Gary A. King, Ph. D, attached hereto as Exhibit 9, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that “the therapeutic benefit and long term safety and tolerability of galanthamine is still a matter for speculation.”

13. All documents concerning any communication or discussion between you and any person concerning the ‘318 patent.

14. All documents concerning any communication or discussion between you and any person concerning galantamine as a treatment for Alzheimer’s Disease.

# EXHIBIT 1

**United States Patent** [19]

**Davis**

[11] **Patent Number:** **4,663,318**

[45] **Date of Patent:** **May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] **Inventor:** Bonnie Davis, 17 Seacrest Dr.,  
Huntington, N.Y. 11743

[21] **Appl. No.:** 819,141

[22] **Filed:** Jan. 15, 1986

[51] **Int. Cl.:** ..... A61K 31/55

[52] **U.S. Cl.:** ..... 514/215

[58] **Field of Search** ..... 514/215

[56] **References Cited**

**PUBLICATIONS**

Chem. Abst. (81)-72615z (1974).

Chem. Abst. (86)-115157z (1977).

Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86,  
pp. 1125-1130.

Kendall et al., J. Chem. & Hospital Pharmacol., (1985)  
10-327-330.

S. Chaplygina et al., J. of Highest Nervous Activity vol.  
XXIV 1976 Issue 5, pp. 1-4.

Krause, J. of Highest Nervous Activity, vol. XXII,  
1974, Issue 4.

*Primary Examiner*—Stanley J. Friedman

*Attorney, Agent, or Firm*—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

**7 Claims, No Drawings**

JAN RAZ-0000001

4,663,318

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## METHOD OF TREATING ALZHEIMER'S DISEASE

### GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

### BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in *Anaesthesia* 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in *Acta Anaesth. Scand.* 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaesthesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K) describe the appearance of  $\theta$ -rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in *Zhurnal Vysheh Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA)* 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

### SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

### DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physical form. For example, it may be administered as its hydrobromide, hydrochloride, methyl-sulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water

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at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5-1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. *Life Sciences* 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrhythmias. In such cases, it may be desirable to

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administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrhythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

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3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

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# EXHIBIT 2

May 22, 1987

Mr. R.W. Michal  
Princeton Pharmaceutical Products  
THE SQUIBB CORPORATION  
P.O. Box 4000  
Princeton, NJ 08540

Dear Mr. Michal:

1. We are writing to you on behalf of a client of ours who has just obtained a patent relating to the treatment of Alzheimer's disease. Such treatment is effected by use of galanthamine hydrobromide, an acetylcholinesterase inhibitor with excellent pharmacological properties.

2. The biochemical hallmark of Alzheimer's disease is the loss of the majority of brain acetylcholine. Additionally, variable deficiencies of other neurochemicals may exist in subpopulations of patients. A substantial subgroup of Alzheimer's patients is likely to respond to an anticholinesterase. However, for many other patients an additional agent may be added to the cholinergic treatment. Nonetheless, even in patients who require combination pharmacotherapy, it is difficult to conceptualize an approach that will not have as an anchor an effective agent to reverse the cholinergic deficit.

3. Galanthamine hydrobromide is a safe, well absorbed acetylcholinesterase inhibitor which reaches predictable plasma levels and rapidly localizes to brain, where effects persist for six hours. It is an ideal agent for the treatment of Alzheimer's disease.

4. Galanthamine is superior to tetrahydroaminoacridine (THA), (a drug of sufficient promise to warrant fast-track status by the FDA) in its lack of toxicity, and resistance to the plasma hydrolases which produce wide variability in THA plasma levels, but is equipotent in direct inhibition of brain cholinesterase. It is superior to physostigmine, the agent with which the initial and multiple confirmatory studies of the effect of cholinesterase inhibition in Alzheimer's disease were

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SYN RAZ-0017564

done, in duration of action and resistance to hydrolases. More important, however, is that peak brain levels of galanthamine are three times higher than plasma. Peak brain levels of physostigmine are only half those of plasma, resulting in much greater peripheral cholinergic side effects relative to central therapeutic effects. These side effects have always limited the administrable dose of physostigmine, and it is to be predicted that substantially greater enhancement of central cholinergic activity will be achievable with galanthamine than was ever possible with physostigmine. Galanthamine has the potential to be much more effective than physostigmine.

A U.S. Patent (No. 4663318) for the use of galanthamine and its derivatives in the treatment of Alzheimer's disease issued on May 5 and applications are pending in European and Asia. Inquiries concerning further information, references and the licensing of this patent are invited. Correspondence may be directed to the undersigned.

Very truly yours,

JR:ct

John Richards

Confidential

SYN RAZ-0017565

# EXHIBIT 3

17 Seacrest Drive  
Huntington, New York 11743  
516-423-3182  
August 3, 1987

Scott Reynes, M.D., Ph.D.  
Director of Clinical Research  
The Squibb Corporation  
Route 206 and Providence Line Road  
Box 4000  
Princeton, New Jersey 08543

Dear Dr. Reynes:

Some time ago, the enclosed letter describing galanthamine hydrobromide for the treatment of Alzheimer's disease was sent to your company. A prompt reply indicated no interest. In July, additional information was sent to me which may be relevant to the evaluation of this compound.

In an animal model of Alzheimer's disease, nucleus-basalis lesioned mice had a significant and long-lasting reversal of their memory deficit in a swim-maze task after administration of galanthamine. The enclosed Neuroscience abstract describes this experiment.

Also enclosed are a copy of the patent, a review of relevant literature, and several reprints. The Tonkopii report demonstrates that galanthamine and tetrahydroaminoacridine (THA) produce equivalent inhibition of cholinesterase in brain tissue homogenates. Beyond that similarity, galanthamine and THA are entirely different. Galanthamine is a competitive inhibitor which binds at the active site and does not inhibit pseudocholinesterase; THA is noncompetitive and binds elsewhere. Further comparisons and references are provided in the review. The Mihailova report documents oral bioavailability, plasma and brain levels, and the direct relationship between administered doses and plasma levels.

As I am currently on the faculty of the Mount Sinai School of Medicine, I have enclosed a statement about this patent from my school.

I would be happy to provide further scientific information as required. Other questions may be directed to my attorney, Mr. John Richards, of Ladas and Parry in New York (212-708-1915).

Yours truly,

*Bonnie M Davis M.D.*

Bonnie M. Davis, M.D.

# EXHIBIT 4

P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 921-4000

 E.R. Squibb & Sons

September 8, 1987

Bonnie M. Davis, M.D.  
17 Seacrest Drive  
Huntington, New York 11743

Dear Dr. Davis:

Thank you for your letter of August 3 concerning galanthamine. I am only now getting settled here at Squibb and able to reply.

I have discussed the situation with our Licensing Division, and we have decided to reconsider galanthamine as a potential licensing-in candidate. This review will take several weeks, after which I will contact you again.

If you have already entered into an agreement with another company on the compound, please notify me as soon as possible. Thank you for bringing this interesting compound to my attention.

Sincerely,



Scott A. Reines, M.D., Ph.D.  
Vice President, International Medical Affairs

/at

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SYN RAZ-0000710

# EXHIBIT 5

P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 921-4610  
Telex: 843334 SQUIBB PRIN  
Rapifax: (609) 921-4149

Gary A. King, Ph.D.  
Associate Scientific Director  
Licensing

REDACTED



E.R. Squibb & Sons

September 30, 1987

Bonnie M. Davis, M.D.  
17 Seacrest Drive  
Huntington, NY 11743

Dear Dr. Davis:

Your letter of August 3rd to Dr. Scott Reines was referred to our department which manages the evaluation of outside products considered for in-licensing.

The proposed licensing candidate, galanthamine HBr, was referred to a committee of staff members concerned with research planning, and drug discovery and development for evaluation. The merits of your proposal, which is both novel and therapeutically relevant, were certainly appreciated. However, I regret to say that galanthamine HBr cannot be considered for in-licensing at this time. This is due to its very early stage of development and the fact that Squibb is not prepared to undertake the very extensive development work that would be required to take this drug into clinical trials.

We appreciate your having brought this opportunity to our attention and giving us the chance to review it. I wish you future success with this project.

Sincerely yours,

  
Gary A. King, Ph.D.

GAK/jpb

REDACTED

# EXHIBIT 6

17 Seacrest Drive  
Huntington, N.Y., 11743  
Phone (516)423-3182  
Fax (516)423-3199  
February 24, 1989

Gary A. King, Ph.D.  
Scientific Director  
Worldwide Licensing and Business Affairs  
E.R. Squibb & Sons  
P.O. Box 4000  
Princeton, N.J. 08543-4000

Dear Dr. King:

Thank you for your interest in galanthamine and analogs.  
Enclosed is information for your review.

1) "Galanthamine for Alzheimer's Disease and Related Dementias,"  
a summary of the properties of galanthamine and its application to  
Alzheimer's disease.

2) "Galanthamine Toxicity," a compilation of literature,  
predominantly English, bearing on the safety and tolerability of  
the drug.

3) Pharmacol Biochem Behav reprint. This is a just-published  
report of galanthamine reversal of the cognitive deficit in nBM-  
lesioned mice. Note how Fig. 4 shows that behavior is still  
significantly improved 24h after one dose.

4) Sweeney et al submitted paper. This is a replication of the  
above study with dose-response data. It demonstrates priming effects  
of each dose on subsequent performance.

5) Sweeney et al Neuroscience poster (1988). This contains all  
of the information prepared for publication in item 4), and  
additional studies on in vivo enzyme kinetics, time course of  
cholinesterase inhibition in brain homogenates, and histologic  
confirmation of basalis lesions.

6) "Galanthamine Analog Structure/Function Summary" You will  
see there are several compounds which could be developed as fully-  
patented entities already synthesized, and the information with  
which to make more. The chemists are continuing this project and  
additional contractual work could be arranged.

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SYN RAZ-0017692

It is possible that galanthamine could be proved efficacious before the analog cases have been considered by certain backlogged foreign patent offices, and that this process could take more than five years. Therefore my attorney asks ten-year confidentiality. I have changed and initialled both forms and I guess you would have to initial the change as well and return one to me. The analog information is in a sealed envelope attached to the confidentiality forms.

The granted use-patent contains specifications for a sustained release formulation. Because the behavioral effects of repeated low doses of galanthamine accumulate, far outlasting plasma levels, the sustained release of low doses of galanthamine might conceivably produce a therapeutic effect with very minimal peripheral cholinergic activity. Current applications describe galanthamine/noradrenergic drug combinations. Preclinical studies indicate that both cholinergic and noradrenergic replacement will be necessary in the 50% of patients with significant locus coeruleus, in addition to their basalis cell loss. Thus, both sustained-release galanthamine, and galanthamine/noradrenergic drug combinations, could be useful formulations.

I am aware of your concerns about preclinical development. However, should you desire to develop an analog, the Coyle laboratory (Sweeney et al), with adequate support, will be able to conduct any subsequent work.

I hope this information is useful. If you have questions, please call, write or fax a message if you call and I'm not in. I'm scheduled to be in New Jersey this Thursday.

Very truly yours,



Bonnie M. Davis, M.D.

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SYN RAZ-0017693

# EXHIBIT 7

P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 921-4000  
Telex: 843334 SQUIBB PRIN  
Rapix: (609) 921-4149 — 921-5360  
  
Gary A. King, Ph.D.  
Scientific Director  
Worldwide Licensing and Business Analysis



**E.R. Squibb & Sons**

October 6, 1989

**Dr. Bonnie Davis  
BJM RESEARCH  
17 Seacrest Drive  
Huntington, New York 11743**

Dr. Bonnie:

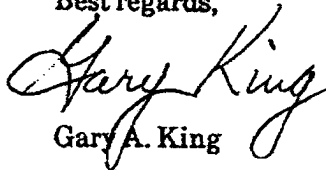
Mr. Ignace Goethals, Vice President for Licensing, and I would like to meet with you next week to further discuss Bristol-Myers Squibb's interest in galanthamine and its analogs. Following my telephone discussion this afternoon with Ken, Ignace and I felt that it would be worthwhile to meet with you to inform you first hand regarding the status of our internal deliberations, and to get a better idea of your own position.

If it will be more convenient for you to meet with us in New York, we can arrange to meet with you in our offices on 57 Street. It will not be possible to meet on Tuesday, and Thursday would be best. However, please let me know what is convenient for you.

Our offices are closed on Monday; however, if you wish you can call me at home on Monday (215-860-2849), or else give me your response by fax or telephone on Tuesday.

In any event, I am looking forward to meeting with you again.

Best regards,

  
Gary A. King

GAK:dw

cc: Mr. I. Goethals

# EXHIBIT 8

P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 921-4000  
Telex: 843334 SQUIBB PRIN  
Rapifax: (609) 921-4149 — 921-5360

Gary A. King, Ph.D.  
Scientific Director  
Worldwide Licensing and Business Analysis



**E.R. Squibb & Sons**

via RAPIFAX  
**CONFIRMATION**

October 10, 1989

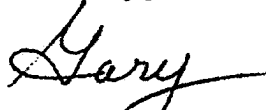
**Dr. Bonnie Davis**  
**BJM RESEARCH**  
17 Seacrest Drive  
Huntington, New York 11743

Dear Dr. Davis:

Thank you for your rapifax of this afternoon. Our meeting on Thursday, October 12, at 10:30 is confirmed. The location will be 40 West 57th Street, Conference Room A. A phone number in New York, in case you need to contact us there on the day of the meeting, is (212) 621-7000. I will be bringing a preliminary time-line for a proposed development plan.

Mr. Goethals and I look forward to seeing you on Thursday. Please plan on joining us for lunch, following our meeting.

Sincerely yours,

  
Gary A. King

cc: Mr. I. Goethals

# EXHIBIT 9

P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 921-4610  
Telex: 843334 SQUIBB PRIN  
Rapifax: (609) 921-6360

Gary A. King, Ph.D.  
Scientific Director  
Worldwide Licensing and Business Analysis

 E.R. Squibb & Sons

December 21, 1989

Dr. Bonnie Davis  
17 Sea Crest Drive  
Huntington, New York 11743

Dear Dr. Davis:

Scientists in our CNS research group have now completed their evaluation of data on galanthamine and its analogues, and, therefore, I am writing to convey the results of that evaluation. The consensus of opinion is that Bristol-Myers Squibb should not seek a license to these compounds at the present time. Our decision is based upon concerns for the clinical and commercial success of galanthamine, and the very early stage of development, and corresponding lack of data for the analogs.

The very narrow therapeutic window that was observed in animal studies with galanthamine was considered to be a significant shortcoming. Impairment of response acquisition is normal mice, at doses that were not different than the dose that reversed behavioral deficits in lesioned animals, also caused concerns for the therapeutic ratio in man. The occurrence of salivation in monkeys at therapeutic doses of galanthamine, also raised similar concerns.

Unfortunately, clinical experience with galanthamine in Alzheimer's patients is, presently, very limited. Therefore, the therapeutic benefit and long term safety and tolerability of galanthamine is still a matter for speculation.

As we have discussed previously, the fact that galanthamine is protected only by use patents, and that marketing exclusivity might only be a certainty in the U.S., means that galanthamine will be of less interest to us than a similar drug protected by composition of matter patents in all major countries.

As a corollary to the above, novel galanthamine analogs could be of greater interest, if more extensive animal testing reveals that these drugs have a broad therapeutic window and a large safety ratio. Therefore, provided that you are still free to discuss these compounds, we may be interested in reviewing the results of future studies.

I regret that we cannot pursue your proposal further at the present time. However, I appreciate very much the earnest cooperation that you have given us, and I wish you continued success.

Sincerely yours,

  
Gary A. King

cc: D. Temple  
J. Vida

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SYN RAZ-0000721

**CERTIFICATE OF SERVICE**

I hereby certify that on the 26th day of May, 2006, the attached **NOTICE OF DEPOSITION AND SUBPOENA OF BRISTOL-MYERS SQUIBB COMPANY PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 45** was served upon the below-named counsel of record at the address and in the manner indicated:

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Young Conaway Stargatt & Taylor, LLP  
The Brandywine Building  
1000 West Street, 17<sup>th</sup> Floor  
Wilmington, DE 19801

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1635 Market Street, 12<sup>th</sup> Floor  
Philadelphia, PA 19103

VIA FEDERAL EXPRESS

*/s/ Tiffany Geyer Lydon*

---

Tiffany Geyer Lydon